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TI    HEPARINASE III AND USES THEREOF
INF   El-Shabrawi; Yosuf, Graz, AT
      Holley; Kristine, Boston, MA, US
      Liu; Dongfang, Framingham, MA, US
      Pojasek; Kevin, Cambridge, MA, US
      Sasisekharan; Ram, Cambridge, MA, US
      Shriver; Zachary, Cambridge, MA, US
      Venkataraman; Ganesh, Wallham, MA, US
IN    El-Shabrawi Yosuf (AT); Holley Kristine; Liu Dongfang; Pojasek Kevin;
      Sasisekharan Ram; Shriver Zachary; Venkataraman Ganesh
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AI    US 2001-802285      20010308
PRAI  US 2000-187846P     20000308 (Provisional)
FI    US 2002122793       20020905
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DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
GOVI (0002) Some aspects of the invention were made with government support under NIH Contract No. GM57073. The government may have certain rights in the invention.
CLMN 60
GI 16 Figure(s).
FIG. 1 is a graph depicting the effect of DEPC inactivation of heparinase III on rate constant.
FIG. 2 is a graph depicting the pH dependence of the second order rate constant of inactivation upon incubation of heparinase III with varying concentrations of DEPC.
FIG. 3 is a graph depicting the quantification of DEPC-**modified histidine** residues in **heparinase** III over a period of time.
FIG. 4 is a graph depicting the substrate protection of heparinase III inactivation by DEPC III.
FIG. 5 is a reverse phase HPLC profile of a lys-C digest of heparinase III which was not exposed to DEPC (top panel) and a peptide profile of heparinase III labeled with DEPC (bottom panel).
FIG. 6 is a series of graphs depicting SAX analysis of exhaustive heparinase III digests of heparan sulfate. Heparan sulfate was digested with either heparinase III from F. heparinum (panel A), recombinant heparinase III (panel B), H295A mutant enzyme (panel C), H510A mutant enzyme (panel D), or the H105A mutant enzyme (panel E).
FIG. 7 depicts a circular dichroism analysis of recombinant heparinase III and the H295A mutant enzyme, and the H510A mutant enzyme.
FIG. 8 is a graph depicting tumor volume in mice, as well as mice treated with heparinase I.
FIG. 9 is a bar graph depicting number of lung nodules that developed 13 days after tail vein injection of B16 BL6 cells. The cells were either treated with PBS, heparinase I, or heparinase III.
FIG. 10, panel A, depicts the tumor volume of mice that were treated with GAG fragments generated from treatment of B16 BL6 cells with either heparinase I, heparinase III, or PBS or fragments generated from heparinase I treatment of LLC cells. Tumor volume was measured over time between 7 and 15 days postinjection of the tumor cells.
FIG. 10, panel B is a bar graph which quantitates the number of lung nodules of the mice described in panel A.
FIG. 11 is a bar graph depicting the effect on B16 cellular migration and invasion of transfection with antisense 20ST in pcDNA3.1.
FIG. 12 shows bar graphs depicting the ability of the transfected cells of FIG. 12 to develop into primary tumors as assessed by mean tumor volume (12a) and tumor weight (12b).
FIG. 13 depicts the results of compositional analysis of HLGAG saccharide fragments released from B16BL6 cells.
FIG. 14 is a bar graph depicting FGF2 signaling modulated by HLGAG fragments
FIG. 15 is a table (15a) and a schematic depicting the modulation of FGF2 activity in vivo by B16BL6 fragments (15b).
AB The invention relates to heparinase III and mutants thereof. Modified forms of heparinase III having reduced enzymatic activity which are useful for a variety of purposes, including sequencing of heparin-like glycosaminoglycans (HLGAGs), removing active heparan sulfate from a solution, inhibition of angiogenesis, etc. have been discovered according to the invention. The invention in other aspects relates to methods of treating cancer and inhibiting tumor cell growth and/or metastasis using heparinase III, or products produced by enzymatic cleavage by heparinase III of HLGAGs.

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TI Heparinase II from Flavobacterium heparinum: Role of histidine residues in enzymatic activity as probed by chemical modification and site-directed mutagenesis.
AU Shriver, Zachary; Hu, Yini; Sasisekharan, Ram (1)
CS (1) MIT, 77 Massachusetts Ave. Build. E18-568, Cambridge, MA 02139 USA
SO Journal of Biological Chemistry, (April 24, 1998) Vol. 273, No. 17, pp. 10160-10167.
ISSN: 0021-9258.
DT Article
LA English
AB The three heparinases derived from Flavobacterium heparinum are powerful tools for studying heparin-like glycosaminoglycans in major biological processes, including angiogenesis and development. Heparinase II is unique among the three enzymes because it is able to catalytically cleave both heparin and heparan sulfate-like regions of heparin-like glycosaminoglycans. Toward understanding the catalytic mechanism of heparin-like glycosaminoglycan degradation by heparinase II, we set out to investigate the role of the histidines of heparinase II in catalysis. We observe concentration-dependent inactivation of heparinase II in the presence of the reversible histidine-modifying reagent diethylpyrocarbonate (DEPC). With heparin as the substrate, the rate constant of inactivation was found to be 0.16 min-1 mM1-1; with heparan sulfate as the substrate, the rate constant was determined to be 0.24 min-1 mM-1. Heparinase II activity is restored following hydroxylamine treatment. This, along with other experiments, strongly suggests that the inactivation of heparinase II by DEPC is specific for histidine residues and that three histidines are modified by DEPC. Substrate protection experiments show that heparinase II preincubation with heparin followed by the addition of DEPC resulted in a loss of enzymatic activity toward heparan sulfate but not heparin. However, heparinase II preincubation with heparan sulfate was unable to protect heparinase II from DEPC inactivation for either of the substrates. Proteolytic mapping studies with Lys-C were consistent with the chemical modification experiments and identified histidines 238, 451, and 579 as being important for heparinase II activity. Further mapping studies identified histidine 451 as being essential for heparin degradation. Site-directed mutagenesis experiments on the 13 **histidines** of **heparinase** II corroborated the chemical **modification** and the peptide mapping studies, establishing the importance of histidines 238, 451 and 579 in heparinase II activity.

L3 ANSWER 3 OF 4 DGENE (C) 2002 THOMSON DERWENT
AN AAY70163 Protein DGENE
TI Modified heparinases, useful for inhibiting angiogenesis, for diminishing the symptoms of psoriasis and for inhibiting cellular proliferation, are rationally designed and based on heparinase I and II of Flavobacterium heparinum -
IN Shriver Z; Venkataraman G; Sasisekharan R; Liu D
PA (MASI) MASSACHUSETTS INST TECHNOLOGY.
PI WO 2000012726 A2 20000309 101p
AI WO 1999-US19841 19990827
PRAI US 1998-98153 19980827
DT Patent
LA English
OS 2000-237884 [20]
AB The present sequence is a Flavobacterium heparinum heparinase II peptide containing His451. DEPC (diethylpyrocarbonate)-modified heparinase II was digested with protease Lys-C for identifying active-site residues. Results identify His451 as the essential **histidine** for heparin breakdown. **Modified heparinases** are useful for studying structure -function relationship of heparin-like glycosaminoglycans and therapeutic purposes. They are also useful for removing active heparin from a heparin containing fluid or active heparan sulphate from a heparan sulphate containing fluid, where the heparinase

is immobilised on a solid support. This is used for inhibiting angiogenesis in tumour, for treating an eye disease characterised by abnormal neovascularisation, psoriasis and for inhibiting cellular proliferation. They are also useful for sequencing heparin or heparan sulphate.

L3 ANSWER 4 OF 4 DGENE (C) 2002 THOMSON DERWENT
AN AAY70162 Protein DGENE
TI Modified heparinases, useful for inhibiting angiogenesis, for diminishing the symptoms of psoriasis and for inhibiting cellular proliferation, are rationally designed and based on heparinase I and II of Flavobacterium heparinum -
IN Shriver Z; Venkataraman G; Sasisekharan R; Liu D
PA (MASI) MASSACHUSETTS INST TECHNOLOGY.
PI WO 2000012726 A2 20000309 101p
AI WO 1999-US19841 19990827
PRAI US 1998-98153 19980827
DT Patent
LA English
OS 2000-237884 [20]
AB The present sequence is a Flavobacterium heparinum heparinase II peptide containing His451. DEPC (diethylpyrocarbonate)-modified heparinase II was digested with protease Lys-C for identifying active-site residues. Results identify His451 as the essential **histidine** for heparin breakdown. **Modified heparinases** are useful for studying structure -function relationship of heparin-like glycosaminoglycans and therapeutic purposes. They are also useful for removing active heparin from a heparin containing fluid or active heparan sulphate from a heparan sulphate containing fluid, where the heparinase is immobilised on a solid support. This is used for inhibiting angiogenesis in tumour, for treating an eye disease characterised by abnormal neovascularisation, psoriasis and for inhibiting cellular proliferation. They are also useful for sequencing heparin or heparan sulphate.